Cont A13

hypercholesterolemia, hyperlipemia, arteriosclerosis, vascular diseases, mycoses, parasite infections, gallstones, tumors and/or hyperproliferative disorders, and/or treatment and/or prophylaxis of impaired glucose tolerance and diabetes, which method comprises administering a therapeutically effective amount of a compound according to claim 1 to a mammal in need of such treatment.

## REMARKS

Claims 1, 24, 25, 43, 44, 47, 49, 51, 53-56, 58, 61, 68, 71, 73 and 75 have been amended. Claim 59 is cancelled. Upon entry of the amendments, claims 1-8, 10-27, 42-58, 60-63 and 67-75 are under consideration. The Examiner has withdrawn claims 9, 28-41 and 64-66 from consideration.

Reconsideration and withdrawal of the rejections are requested.

The Examiner has restricted the claims under 35 USC § 121. Applicants affirm the election of Group I, claims 1-8, 10-27, 42-63 and 67-75 where W and X represent $SO_2$ or $SO_2NR^1$. Applicants also affirm the election of the compound of Example 17.6 as species. In effect, the Examiner has made an intraclaim restriction requirement. Contrary to the Examiner's position, Applicants submit that the requirement is improper.

The U.S. Patent Office is required to examine on the merits the entirety of generic claims. As set forth in MPEP § 809.02, the U.S. Patent Office is required to perform a search for all claims readable on the elected species. If the elected species is found patentable, then subsequent

species should be examined. If no species is found unpatentable, then the generic claim should be allowed. The MPEP does not authorize the Patent Office to derive its own concept of a genus from claim 1 and require that it be carved out of existing claims.

Applicants point out that it is well-established law that restriction within a single claim cannot be sustained under 35 U.S.C. §121. As is stated in *In re Weber*, 198 USPQ 328 (CCPA 1978), at pages 331-332:

> "§121 provides the Commissioner with the authority to promulgate rules designed to *restrict an application* to one of several claimed inventions when those inventions are found to be "independent and distinct." It is not, however, provide a basis for the Examiner acting under the authority of the Commissioner to *reject* a particular *claim* on that same basis." (Emphasis in original text.)

If the Patent Office were to withdraw applicants' claims in part from further consideration due to an intraclaim restriction, the requirement amounts in fact to a rejection, see *In re Hass*, 179 USPQ 623, 625 (CCPA 1973).

Applicants have the right under U.S. patent law to claim their invention using the limitations that they regard as essential to delineate the invention, as long as the requirements of 35 U.S.C. §112 are met. See *In re Weber* at 331 and *In re Wolfrum and Gold*, 179 USPQ 620, 622 (CCPA 1973).

In view of the above, Applicants request that the restriction requirement be withdrawn. In particular, Applicants request that the intra-claim restriction requirements be withdrawn since

such restriction is prohibited both under the law and under Patent Office policy as set forth in the MPEP.

In view of the above, Applicants also note the impropriety of the Examiner's intended action of subjecting Group II claims to (intraclaim) restriction based on the values of W and X. Applicants also maintain the right to traverse any future such requirement, once made.

The Examiner has rejected claims 1-8, 10-27, 42-63 and 67-75 under 35 USC § 112, second paragraph as indefinite. The Examiner argues that in claims 1 and 24 as well as in claims 43, 44, 47, 49, 51, 53-58, 61 and 68-71, the term "pharmaceutically acceptable esters" is indefinite since it is not clear how the ester is being formed. Applicants note that the specification at page 8, paragraph [0026], describes "pharmaceutically acceptable esters" as "esters of the compounds of formula (I), in which hydroxy groups have been converted to the corresponding esters....." Independent claims 1 and 24 properly embrace "pharmaceutically acceptable esters" of formula (I) and formula (Ia), respectively, because the substituents $A^2$ and $R^2$ of claim 1, and substituent $A^{12}$ of claim 24, may have hydroxy.

In claims 43, 44, 47, 49, 51, 53-58, 61 and 71, "pharmaceutically acceptable esters" of the recited compounds have been deleted.

In claims 69 and 70, "pharmaceutically acceptable esters" can be made from the ethanol group of the recited compounds. Claim 25, upon which claims 69-70 depend, has been amended to recite that $A^{12}$ may be lower alkyl substituted with hydroxy. Support is obtained from original claim 24 and page 11, paragraph [0036], under the definition of $A^{12}$.

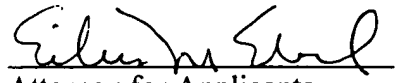
In response to the Examiner's rejection of claim 73, the claim has been amended to replace the term "manufacture" with --- preparation --- .

Regarding claim 75, the term "2,3-oxidosqualine: lanosterol cyclase" has been added by amendment with reference to the abbreviation OSC, in accordance with the disclosure at page 2, paragraph [0006], line 3. Applicants have also made the other amendments suggested by the Examiner to claim 75. An additional amendment has been made at the end of the claim to conform to the amendment reciting diseases "in a mammal".

The Examiner objects to claims 1-7, 10-27, 60, 62, 63 and 73-75 as directed to Improper Markush Group. Independent claims 1 and 24 have been amended to remove the Markush format of claiming. In accordance with the remarks above in response to the requirement for restriction, Applicants are not required by law to amend the claims to read upon the elected group.

A Petition for Extension of Time – 2 months – is enclosed. If any required fees are missing or insufficient, please charge our Deposit Account No. 08-2525.

Respectfully submitted,



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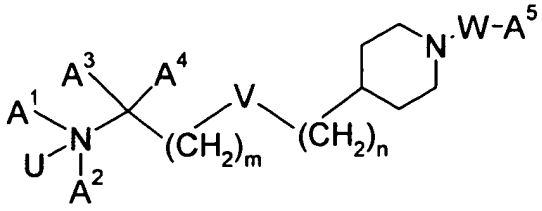
VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) A compound ~~selected from the group consisting of compounds~~ of formula (I)



(I)

wherein

U is O or a lone pair;

V is O, $-CH_2-$, -CH=CH-, or $-C\equiv C-$;

m and n are each integers from 0 to 7 and m+n is 0 to 7;

W is CO, COO, $CONR^1$, CSO, $CSNR^1$, $SO_2$, or $SO_2NR^1$, with the provisos that:

a) V is not $-CH_2-$ when W is CO,

b) m+n is 1 or 2 when V is $-CH_2-$ and W is $SO_2$,

c) m=n=0 when V is –CH=CH- and W is CO or $SO_2$,

d) m is 1 to 7 when V is O, and

e) m is 1 to 3 when V is O, W is CO or $SO_2$, and n is 0;

$A^1$ is H, lower-alkyl or lower-alkenyl,

$A^2$ is cycloalkyl, cycloalkyl-lower-alkyl, lower-alkenyl, lower-alkynyl or lower-alkyl optionally substituted with hydroxy, lower-alkoxy or lower-alkoxy-carbonyl, or

$A^1$ and $A^2$ bond together to form $-A^1-A^2-$, wherein $-A^1-A^2-$ is lower-alkylene or lower-alkenylene, optionally substituted by $R^2$, and one $-CH_2-$ group of $-A^1-A^2-$ is optionally replaced by $NR^3$, S, or O;

$A^3$ and $A^4$ are independently hydrogen or lower-alkyl;

$A^5$ is lower-alkyl optionally substituted with halogen, lower-alkenyl, lower-alkoxy-carbonyl-lower-alkyl, cycloalkyl, cycloalkyl-lower-alkyl, aryl, aryl-lower-alkyl, heteroaryl, or heteroaryl-lower-alkyl;

$R^2$ is lower-alkyl, hydroxy, hydroxy-lower-alkyl, or $N(R^4,R^5)$;

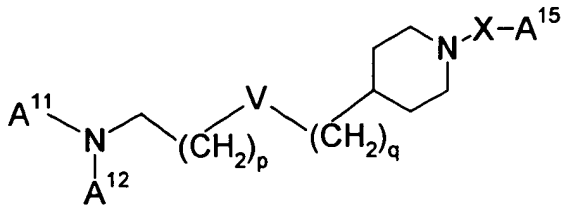
$R^1$, $R^3$, $R^4$ and $R^5$ are independently hydrogen or lower-alkyl; and

When $A^1$ is not bonded to $A^2$, $A^1$ and $A^3$ optionally bond together to form $-A^1-A^3-$, wherein $-A^1-A^3-$ is lower-alkylene or lower-alkenylene, optionally substituted by $R^2$, and one $-CH_2-$ group of $-A^1-A^3-$ is optionally replaced by $NR^3$, S, or O; or

pharmaceutically acceptable salts or esters of the compounds of formula (I)., ~~and~~

~~pharmaceutically acceptable esters of the compounds of formula (I).~~

24. (Amended) A compound ~~selected from the group consisting of compounds~~ of formula (Ia)




(Ia)

wherein

V is O, $-CH_2-$, -CH=CH-, or -C≡C-;

p is an integer from 0 to 5;

q 0, 1 or 2;

X is CO, COO, $SO_2$, or $SO_2NH$, with the provisos that:

a) V is not $-CH_2-$ when X is CO,

b) p+q is 1 or 2 when V is $-CH_2-$ and X is $SO_2$,

c) p=q=0 when V is -CH=CH- and X is CO or $SO_2$,

d) p is 1 to 5 when V is O, and

e) p is 1 to 3 when V is O, X is CO or $SO_2$, and q is 0;

$A^{11}$ is methyl or ethyl;

$A^{12}$ is cyclopropyl, lower-alkenyl, or lower-alkyl optionally substituted with hydroxy or lower-alkoxy; and

$A^{15}$ is lower-alkyl optionally substituted with halogen, lower-alkenyl, lower-alkoxy-carbonyl-lower-alkyl, cycloalkyl, cycloalkyl-lower-alkyl, aryl, aryl-lower-alkyl, heteroaryl, or heteroaryl-lower-alkyl; or

pharmaceutically acceptable salts or esters of the compounds of formula (Ia)., ~~and~~

~~pharmaceutically acceptable esters of the compounds of formula (Ia).~~

25. (Amended) The compound of claim 24, wherein $A^{12}$ is cyclopropyl, lower alkenyl of 2 to 4 carbon atoms, lower alkyl of 1 to 4 carbon atoms, lower alkoxy of 1 to 4 carbon atoms, ~~or a~~ lower alkyl substituted with a lower-alkoxy having a total of 2 to 4 carbon atoms, or lower alkyl substituted with hydroxy.

43. (Amended) The compound of claim 42, selected from the group consisting of allyl-{4-[1-(4-chloro-benzenesulfonyl)-piperidin-4-yloxy]-butyl}-methyl-amine, and pharmaceutically acceptable salts thereof ~~and pharmaceutically acceptable esters thereof~~.

44. (Amended) The compound of claim 42, selected from the group consisting of allyl-{3-[1-(4-bromo-benzenesulfonyl)-piperidin-4-yloxy]-propyl}-methyl-amine, and pharmaceutically acceptable salts thereof ~~and pharmaceutically acceptable esters thereof~~.

47. (Amended) The compound of claim 46, selected from the group consisting of 4-[6-(allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid butylamide, and pharmaceutically acceptable salts thereof ~~and pharmaceutically acceptable esters thereof~~.

49. (Amended) The compound of claim 48, selected from the group consisting of 4-[6-(allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid cyclohexylmethyl-amide, and pharmaceutically acceptable salts thereof ~~and pharmaceutically acceptable esters thereof~~.

51. (Amended) The compound of claim 50, selected from the group consisting of 4-[6-(allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (phenyl)-amide, and pharmaceutically acceptable salts thereof ~~and pharmaceutically acceptable esters thereof~~.

53. (Amended) The compound of claim 52, selected from the group consisting of 4-[6-(allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (4-chloro-phenyl)-amide, and pharmaceutically acceptable salts thereof ~~and pharmaceutically acceptable esters thereof~~.

54. (Amended) The compound of claim 52, selected from the group consisting of 4-[6-(allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (4-bromo-phenyl)-amide, and pharmaceutically acceptable salts thereof ~~and pharmaceutically acceptable esters thereof~~.

55. (Amended) The compound of claim 52, selected from the group consisting of 4-[6-(cyclopropyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (3,4-difluoro-phenyl)-amide, pharmaceutically acceptable salts thereof ~~and pharmaceutically acceptable esters thereof~~.

56. (Amended) The compound of claim 52, selected from the group consisting of 4-[6-(allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (2,5-difluoro-phenyl)-amide, and pharmaceutically acceptable salts thereof ~~and pharmaceutically acceptable esters thereof~~.

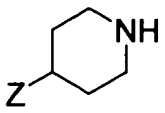
58. (Amended) The compound of claim 57, selected from the group consisting of 4-[6-(allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (4-trifluoromethyl-phenyl)-amide, pharmaceutically acceptable salts thereof ~~and pharmaceutically acceptable esters thereof~~.

61. (Amended) The compound of claim 60, selected from the group consisting of methyl-propyl-{4-[1-(4-trifluoromethyl-benzenesulfonyl)-piperidin-4-yl]-butyl}-amine, and pharmaceutically acceptable salts thereof ~~and pharmaceutically acceptable esters thereof~~.

68. (Amended) The compound of claim 67, selected from the group consisting of methyl-propyl-{3-[1-(4-trifluoromethyl-benzenesulfonyl)-piperidin-4-yl]-prop-2-ynyl}-amine, and pharmaceutically acceptable salts thereof ~~and pharmaceutically acceptable esters thereof~~.

71. (Amended) The compound of claim 67, selected from the group consisting of ethyl-(2-methoxy-ethyl)-{4-[1-(4-trifluoromethyl-benzenesulfonyl)-piperidin-4-yl]-but-3-ynyl}-amine, and pharmaceutically acceptable salts thereof ~~and pharmaceutically acceptable esters thereof~~.

73. (Amended) A process for the ~~manufacture~~ preparation of compounds according to claim 1, which process comprises reacting a compound of formula (II)




(II)

wherein Z is $(A^1,A^2)N\text{-}C(A^3,A^4)\text{-}(CH_2)_m\text{-}V\text{-}(CH_2)_n\text{-}$, $X\text{-}CH_2\text{-}(CH_2)_m\text{-}V\text{-}(CH_2)_n\text{-}$, $HO(CH_2)_n\text{-}$, or $HOOC(CH_2)_n\text{-}$, wherein X is chlorine, bromine, iodine, methanesulfonyl, or toluenesulfonyl, and $A^1$, $A^2$, $A^3$, $A^4$, V, m and n are as defined in claim 1,
with $ClSO_2\text{-}A^5$, $ClCOO\text{-}A^5$, $ClCSO\text{-}A^5$, $OCN\text{-}A^5$, $SCN\text{-}A^5$, $HOOC\text{-}A^5$, or $ClSO_2NR^1\text{-}A^5$, wherein $A^5$ is as defined in claim 1.

75. (Amended) A method for the treatment and/or prophylaxis of diseases in a mammal which are associated with 2,3-oxidosqualene: lanosterol cyclase (OSC) such as hypercholesterolemia, hyperlipemia, arteriosclerosis, vascular diseases, mycoses, parasite infections, gallstones, tumors and/or hyperproliferative disorders, and/or treatment and/or prophylaxis of impaired glucose tolerance and diabetes, which method comprises administering a therapeutically effective amount of a compound according to claim 1 to a mammal in need of such treatment ~~human being or animal~~.